CHAPTER 1

The Pharmacology of Psychedelics

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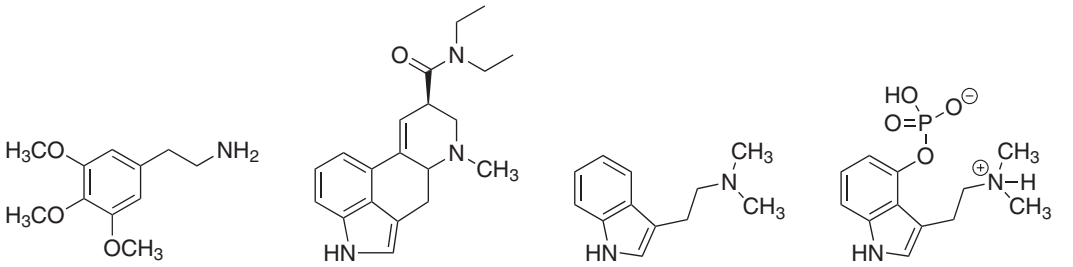
Introduction

We focus in this chapter on what have been called *serotonergic hallucinogens, classic hallucinogens,* or more simply *psychedelics*. Many written reviews have included detailed discussion of the pharmacology of psychedelics (Halberstadt, 2015; Nichols, 2016; Passie, Halpern, Stichtenoth, Emrich, & Hintzen, 2008; Passie, Seifert, Schneider, & Emrich, 2002). Most of these include much of the historical understanding of the pharmacology of these substances, but in the context of this chapter, we do not believe it is particularly important to review historical studies extensively; the interested reader can consult the previously cited reviews for comprehensive discussions. Rather, it seems more useful to provide up-to-date knowledge derived from recent studies and to distill the information down into its essential points. Nonetheless, some brief background is warranted to place the chapter in context.

The earliest rigorous scientific work on a psychedelic was Dr. Arthur Heffter's (1898) classic experiment with the peyote cactus, *Lophophora williamsii*. Through systematic chemical investigations, he was able to isolate the major alkaloids from the peyote cactus. He subsequently self-administered each of the individually isolated alkaloids, thereby identifying mescaline (Figure 1.1), as the psychoactive component. Following the synthesis of mescaline in 1919 (Späth, 1919), this substance was the subject of self-experiments by numerous artists, scientists, philosophers, writers, and others for the next 50 years.

The next chapter of this story involves the accidental 1943 discovery of the psychoactive properties of lysergic acid diethylamide (LSD) by Dr. Albert Hofmann (1979), a natural products chemist working at the Sandoz Laboratories in Basel, Switzerland). He had first synthesized LSD in 1938 while developing ergot derivatives that might have therapeutic utility. In subsequent years, Hofmann carried out numerous scientific studies of South American intoxicating plants, culminating in the identification and synthesis of psilocybin, the active component in psilocybin mushrooms, which had been known by the Aztecs as *teonanacatl,* translated as "flesh of the gods" (Hofmann, Frey, Ott, Petrzilka, & Troxler, 1958; Hofmann, Heim, Brack, & Kobel, 1958). He was then able to demonstrate that the Aztec preparation known as *ololuiqui,* the seeds from a species of morning glory (*Rivea corymbosa*), contained lysergic acid amide (ergine;



■ **FIGURE 1.1.** The chemical structures of mescaline, LSD, DMT, and psilocybin.

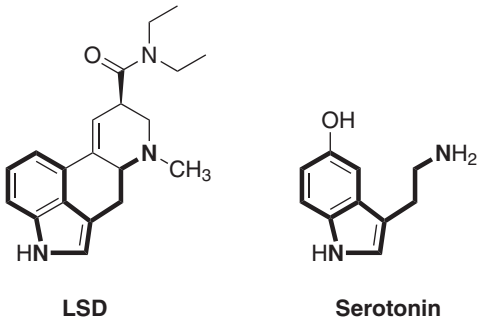
the ethyl groups of LSD have been replaced by hydrogen atoms) as its active psychoactive principle (Hofmann & Tscherter, 1960). Ergine has weak LSD-like properties, but *ololiuqui* was apparently used by the Aztecs when psilocybin mushrooms were in short supply.

A fourth hallucinogen, *N,N*-dimethyltryptamine (DMT), has gained recent popularity through the use of a plant decoction known as ayahuasca. This plant extract is prepared by boiling pounded *Banisteriopsis caapi* vines with leaves from *Psychotria viridis* (McKenna, Towers, & Abbott, 1984; Schultes & Hofmann, 1980). *Psychotria* leaves contain DMT, which is not orally active. However, *Banisteriopsis* contains beta-carboline alkaloids that inhibit liver monoamine oxidase (MAO), and ingestion of the mixture allows the DMT to enter the systemic circulation without being broken down in the liver. Ayahuasca has presumably been used for millennia by indigenous Amazonian peoples, but most recently it has been incorporated into syncretic religions that use it as a sacrament, in particular the União de Vegetal and the Santo Daime. Although DMT is a Schedule 1 controlled substance, the churches that use ayahuasca in their services have been given legal protection by a 2006 Supreme Court decision (*Gonzales v. O Centro Espírita Beneficente União do Vegetal*).

The psychological effects produced by psychedelics are highly subjective, usually including changes in thought and mood, depersonalization, and perceptual alterations that may include visual hallucinations, synesthesias, and tactile sensations. The subjective effects of serotonergic psychedelic hallucinogens are easily distinguished from those of other drug classes also called hallucinogens, such as *N*-methyl-D-aspartate (NMDA) receptor antagonists (e.g., phencyclidine, ketamine), κ-agonists (e.g., salvinorin A), and cannabinoids, which can also produce psychoactive effects. Because of these differences, we now distinguish serotonergic hallucinogens from other hallucinogens by categorizing them as psychedelics.

The profound psychoactive effects of these substances suggested that their biological target(s) must play an extremely important role in normal consciousness and perception, although elucidation of the nature of these targets took many years of research. Hints of their pharmacology were gleaned shortly after the discovery of the powerful psychoactive properties of LSD in 1943. In 1953, serotonin, which was first identified in 1949, was first detected in mammalian brain (Twarog & Page, 1953). Prior to that discovery, it was widely believed that serotonin was found only in the blood, and in the enteric nervous system, within chromaffin cells in the intestines where it was known to regulate vascular and intestinal tone. The realization that LSD was built upon a tryptamine molecular scaffold, as was serotonin (Figure 1.2), led to groundbreaking hypotheses that mental disorders like schizophrenia might be a result of disturbed serotonin function in the brain (Woolley & Shaw, 1954).

Soon after the discovery of LSD it was recognized that there are similarities between the effects of psychedelics and the symptomatology of schizophrenia, and LSD and mescaline were used experimentally to produce a model psychosis. Indeed, Sandoz laboratories distributed LSD as an experimental drug (Delysid) that mental health profes-



■ **FIGURE 1.2.** LSD and serotonin.

sionals could take to gain insight into the minds of their psychotic patients.

Research on the functions of serotonin in the brain rapidly increased in the subsequent years (see, e.g., Freedman, 1961; Rosecrans, Lovell, & Freedman, 1967). It also was discovered early on that LSD, mescaline, and psilocybin all produce a very rapid tolerance to their effects, known as tachyphylaxis, and generally produced cross-tolerance to each other (Appel & Freedman, 1968; Freedman, Aghajanian, Ornitz, & Rosner, 1958; Isbell, Wolbach, Wikler, & Miner, 1961). These findings led investigators to search for the common pharmacological target(s) of the various chemotypes.

Anden, Corrodi, Fuxe, and Hokfelt (1968) first proposed that LSD has a direct *agonist* action at brain serotonin receptors. It was soon discovered that LSD and other indoleamine psychedelics potently inhibit the firing of serotonergic neurons in the dorsal raphe nucleus (DRN) (Aghajanian, Foote, & Sheard, 1968, 1970). These cells send ascending serotonin projections to all parts of the forebrain and decreases in their rate of firing therefore attenuate serotonin biosynthesis and release throughout their projection areas. Indoleamine hallucinogens directly inhibit firing in many DRN target regions, but at low doses preferentially inhibit DRN cells while leaving downstream neurons virtually unaffected (DeMontigny & Aghajanian, 1977; Haigler & Aghajanian, 1974). The finding that hallucinogens are more potent at presynaptic than at postsynaptic sites led to the hypothesis that by depressing the activity of neurons in the DRN and thereby decreasing 5-hydroxytryptamine (5-HT) outflow, psychedelic drugs removed the tonic inhibition of downstream neurons mediated by serotonin.

Further research, however, identified significant problems with this "presynaptic hypothesis" of hallucinogen action. One of the most serious problems was the finding that phenylalkylamine psychedelics such as mescaline did not consistently depress DRN firing (Haigler & Aghajanian, 1973; Penington & Reiffenstein, 1986). Although LSD and indoleamine psychedelics induced a dramatic reduction in nerve impulse flow of serotonergic neurons whether applied microiontophoretically or systemically, mescaline had a suppressant effect in the DRN only when given systemically (Haigler & Aghajanian, 1973). Penington and Reiffenstein (1986) concluded that because both LSD and mescaline can inhibit raphe cells when given systemically, but only LSD readily produced an inhibition in these cells when applied microiontophoretically, the two drugs differed in their mode of action on raphe cells. In addition, certain drugs that were not hallucinogenic also attenuated raphe call firing. For these reasons, the idea that psychedelics acted presynaptically to attenuate raphe cell firing was abandoned as a general mechanism of action.

The ability to inhibit DRN cell firing has proven to be a pharmacological effect unrelated to hallucinogenesis. Nonetheless, the 5-HT_{1A} agonist activity of some indoleamines may contribute to their behavioral action. This effect will be explored in more detail later in this chapter.

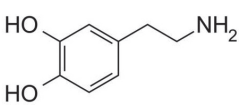
■ The Key Role of the 5-HT_{2A} Receptor

Early investigations sought to determine how interactions with specific neurotransmitter systems contribute to the effects of hallucinogens in humans. A few early studies addressed this issue by attempting to block the effects of LSD with serotonin, dopamine, and norepinephrine receptor antagonists (Isbell & Logan, 1957; Isbell, Logan, & Miner, 1959). Unfortunately, because of the lack of high-affinity receptor-selective antagonists, those studies failed to link the action of hallucinogens to any particular transmitter system.

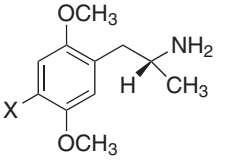
Based on physiological preparations and crude pharmacological tools, two receptors for serotonin were initially identified and named D and M. As pharmacological tools became more sophisticated, it soon became apparent that there were several other forms of serotonin receptors. As these were identified, the D receptor was renamed the 5-HT_2 receptor, and the M receptor became 5-HT_3. Glennon, Young, and Rosecrans first proposed in 1983 that the behavioral effects of hallucinogens are mediated by activation of the 5-HT_2 receptor. This proposal was based on the finding that the high-affinity, selective 5-HT_2 antagonists pirenperone and ketanserin are highly effective in blocking the discriminative stimulus properties of 2,5-dimethoxy-4-methylamphetamine (DOM) and LSD (Colpaert & Janssen, 1983; Colpaert, Niemegeers, & Janssen, 1982), and of DOM-stimulus generalization to LSD, mescaline, and 5-methoxy-*N*,*N*-dimethyltryptamine (5-MeO-DMT; Glennon, Young, Jacyno, Slusher, & Rosecrans, 1983). It was subsequently demonstrated that a robust linear correlation (r = .938) exists between the 5-HT_2 affinities of a series of phenylalkylamine hallucinogens and their effective dose 50 (ED_{50}) values for substitution in animals trained with DOM (Glennon, Titeler, & McKenney, 1984).

Molecular biology enabled the discovery that the 5-HT_2 receptor was actually a family of three closely related receptors. Cloning of the 5-HT_{2C} (originally named the 5-HT_{1C}) and 5-HT_{2A} receptors in 1988 and 1990, respectively, allowed for the development of antagonist ligands that were specific for one receptor or the other. An antagonist correlation analysis demonstrated a strong correlation between the 5-HT_{2A} affinity of a series of 5-HT antagonists and their potencies for blocking LSD stimulus generalization to *R*-(–)-2,5-dimethoxy-4-methylamphetamine (DOM) (Fiorella, Rabin, & Winter, 1995). Furthermore, stimulus control in animals trained with LSD (Winter, Eckler, & Rabin, 2004), 2,5-dimethoxy-4-iodoamphetamine (DOI) (Schreiber, Brocco, & Millan, 1994; Smith, Barrett, & Sanders-Bush, 1999), and DOM (Li, Rice, & France, 2008) was blocked by *M100907,* a highly selective 5-HT_{2A} antagonist. Figure 1.3 illustrates the structures of the *R* enantiomers of DOM, 2,5-dimethoxy-4-bromoamphetamine (DOB), and DOI. Taken together, these findings demonstrated that interactions with the 5-HT_{2A} receptor are required for psychedelics to induce discriminative stimulus effects. Clinical studies also have shown that the effects of psychedelics in humans are blocked by the antagonist ketanserin, which is selective for 5-HT_{2A} receptors in humans (Preller et al., 2017; Vollenweider, Vollenweider-Scherpenhuyzen, Babler, Vogel, & Hell, 1998).

Extensive research has clearly demonstrated that psychedelics are agonists or partial agonists at the brain serotonin 5-HT_{2A} receptor subtype (see recent review by Nichols, 2016). This receptor is a member of the Family A type G-protein-coupled receptors (GPCRs) and is widely expressed throughout the brain. The 5-HT_{2A} receptor is a $G_{q/11}$-coupled receptor that is linked to the phosphoinositide hydrolysis signaling cascade, with formation of diacylglycerol and mobilization of intracellular calcium (Barker, Burris, & Sanders-Bush, 1991; Nichols & Nichols, 2008). The 5-HT_{2A} receptor is excitatory and can cause neuronal cell depolarization when activated by a psychedelic. Members of both the indoleamine and phenylalkylamine classes of hallucinogens are high-affinity agonists or partial agonists at 5-HT_{2A} receptors. Phenylalkylamine hallucinogens such as DOM, DOI, and DOB are highly selective for 5-HT_2 receptor subtypes (Pierce & Peroutka, 1989; Titeler, Lyon, & Glennon, 1988), and there is a consensus in the literature that the behavioral effects of



Dopamine (3,4-dihydroxyphenethylamine)



X = CH_3; (R)-DOM
X = Br; (R)-DOB
X = I; (R)-DOI

■ **FIGURE 1.3.** The structures of the (*R*)-(–)-enantiomers of DOM, DOB, and DOI.

psychedelics are primarily mediated by the 5-HT_{2A} receptor (Halberstadt, 2015; Nichols, 2016).

Expression of 5-HT_{2A} receptors occurs throughout the brain, but their highest expression is found in an enigmatic structure known as the claustrum, a thin, irregular sheet of neurons that is attached to the underside of the neocortex in the center of the mammalian brain. There is also high expression of 5-HT_{2A} receptors in apical dendrites of Layer 5 pyramidal cells in the medial prefrontal and anterior cingulate cortex, as well as in the reticular nucleus of the thalamus, ventral tegmental area, the locus coeruleus, amygdala, and several other important regions. Widespread changes in neuronal excitability resulting from activation of 5-HT_{2A} receptors in these key brain areas would thus be expected to have marked effects on cognition and perception.

Activation of 5-HT_{2A} receptors on glutamatergic pyramidal neurons within the brain by psychedelics, however, generally does not lead to depolarization and the generation of action potentials. Instead, the presence of psychedelics has been shown to increase glutamate release from depolarized neurons to generate what has been termed *recurrent activity* (Aghajanian & Marek, 2000). Interestingly, however, Beique, Imad, Mladenovic, Gingrich, and Andrade (2007) first reported on a subpopulation of large neurons in deep layers of the cortex that was highly sensitive to 5-HT and that responded with strong membrane depolarizations that were capable of initiating spiking activity. The nature of this cell population remained unknown until one of us (C. D. N.; see Martin & Nichols, 2016) was able to purify psychedelic-activated neurons from rat brain for the first time and demonstrate that psychedelics directly activated only a small subset of 5-HT_{2A}-expressing excitatory neurons (<5% of the total brain neuronal population) in key brain regions, including the prefrontal cortex (PFC) and the claustrum. Interestingly, the neurons activated by psychedelics express significantly higher levels of the gene for the 5-HT_{2A} receptor and are therefore likely to be more sensitive to psychedelics than other neurons.

Martin and Nichols (2016) also found that the nature of how psychedelics activated these neurons differed depending on the specific brain region in which they were expressed. They hypothesize that this small population of directly responding neurons represents a "trigger population," and that activation of these neurons initiates cellular events that lead to recurrent activity, cortical network destabilization, and the host of perceptual and cognitive behaviors associated with psychedelics. For example, these activated neurons subsequently recruit other select cell types including small subpopulations (<10%) of inhibitory somatostatin- and parvalbumin-containing γ-aminobutyric acid (GABA)ergic interneurons. The differential activation of subsets of both excitatory and inhibitory neurons in ways that would not occur in a normal conscious brain likely alters the basic function of a given brain area and its ability to communicate with other regions. Because distinct regional cellular populations respond differently to psychedelics, different brain regions are more or less sensitive to their effects. These cellular effects of psychedelics, therefore, likely underlie the alterations in brain network communication observed by recent imaging studies.

Another interesting finding by Martin and Nichols (2016) is that psychedelics also activate astrocytes and glia. Astrocytes function as an interface between synaptic activity and the vasculature, helping to serve the metabolic needs of the neurons. One could speculate that the effects of psychedelics on astrocytes could be contributing to alterations in cortical blood flow and metabolism detected by blood oxygen level–dependent (BOLD) functional magnetic resonance imaging (fMRI) and positron emission tomography (PET), and that blood flow and metabolism may be decoupled through astrocyte activation.

The claustrum, with the highest density of 5-HT_{2A} receptor expression in the entire brain, is an especially intriguing brain structure. Its exact functions remain unclear, but based on patterns of retrograde tracing in nonhuman primates, Reser and colleagues (2014) have suggested that the claustrum is ideally positioned as a modulator that could desynchronize or terminate correlated activation of default mode network (DMN)-related areas. Seeley and colleagues (2007) also propose that the connectivity and anat-

omy of the claustrum place it ideally to control temporal structure of network activity.

Most recently, the crucial role of the 5-HT_{2A} receptor in the clinical actions of psychedelics has been confirmed by clinical studies in which the psychoactive effects of psilocybin, and of LSD, have been blocked by preadministration of ketanserin, an antagonist that is selective for 5-HT_{2A} receptors in humans (Barrett, Preller, Herdener, Janata, & Vollenweider, 2018; Kometer, Schmidt, Jancke, & Vollenweider, 2013; Kraehenmann, Pokorny, Vollenweider, et al., 2017; Preller et al., 2017; Vollenweider et al., 1998).

Safety of Psychedelics

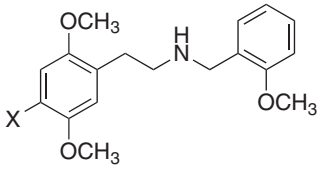
Surprisingly, despite the profound psychoactive effects that psychedelics produce, they are generally physiologically very safe. The classic serotonergic hallucinogens do not lead to dependence, and do not result in overdose deaths after reasonable dosages. Furthermore, single high-acute doses of psychedelics such as LSD do not lead to any molecular or genetic signs of toxicity in rodent models (Nichols & Sanders-Bush, 2002). The incidence of adverse effects is very low when these drugs are used in a controlled, supervised clinical environment (Strassman, 1984). LSD has led to only two reported overdose deaths, and those followed *massive* dosages (Nichols & Grob, 2018). Indeed, eight subjects who mistakenly insufflated LSD, believing it was cocaine, all fully recovered after a few days of medical treatment (Klock, Boerner, & Becker, 1975).

An exception to the safety of classic hallucinogens is the class of drugs referred to as "NBOMe" compounds (Figure 1.4). These compounds are *N*-benzyl derivatives of 2,5-dimethoxy-4-substituted phenethylamines, first discovered by Ralf Heim (2003; Heim & Elz, 2000; Heim, Pertz, & Elz, 1999). They were found to have extraordinarily potent activity at the 5-HT_{2A} receptor (Braden & Nichols, 2007; Braden, Parrish, Naylor, & Nichols, 2006; Rickli et al., 2015). Extensive structure–activity studies on these molecules have been reported by Hansen and colleagues (2014).

Unfortunately, due to their extraordinary potency, as well as their relative ease of synthesis, these compounds are often misrepresented as LSD and have led to numerous emergency room admittances and deaths (Andreasen et al., 2015; Morini et al., 2017; Poklis et al., 2014; Suzuki, Poklis, & Poklis, 2014; Walterscheid et al., 2014). Although the exact cause of death following NBOMe ingestion is not known, 29 cases published in the literature of acute toxicity associated with the use of an NBOMe commonly reported symptoms that include tachycardia (96.6%), hypertension (62.0%), agitation/aggression (48.2%), seizures (37.9%), and hyperthermia (27.6%) (Wood, Sedefov, Cunningham, & Dargan, 2015). Acute kidney injury also has been reported. Because these are processes not normally controlled by 5-HT_{2A} receptor function, this toxicity is likely mediated by activity at other biological targets that remain unknown.

Animal Models to Study Psychedelics

A large amount of the knowledge we have about the mechanism of action of psychedelics has been derived from preclinical studies, either *in vitro* or *in vivo* animal models. The use of animal models to study these compounds has been recently reviewed (Hanks & Gonzalez-Maeso, 2013). Here we discuss only the most widely used and productive animal models: drug discrimination, the mouse head twitch response (HTR), and locomotor measures.



X = Cl; 25C-NBOMe
X = Br; 25B-NBOMe
X = I; 25i-NBOMe

FIGURE 1.4. Structures of the most common NBOMe compounds.

Drug Discrimination

Probably the most detailed information about the mechanism of action of psychedelic drugs has come from extensive drug discrimination studies. Rats can be trained to discriminate the subjective effects of drugs from saline using two-lever operant procedures (Glennon, Rosecrans, & Young, 1982, 1983; Hirschhorn & Winter, 1971). Drug discrimination is a sensitive and robust behavioral technique to assess the nature of the enteroceptive cue produced by central nervous system (CNS)-active drugs. Cross-generalization occurs between training drugs of different chemotypes (e.g., mescaline and LSD), indicating that they produce similar if not identical interoceptive stimulus effects. By contrast, other drug classes fail to evoke psychedelic-like stimulus effects reliably (Appel & Cunningham, 1986; Glennon et al., 1982; Glennon, Rosecrans, et al., 1983). The major limitation of drug discrimination is the need for several months of animal training prior to any testing experiments. Once animals have been trained to recognize a particular cue (e.g., LSD), other compounds can be tested to determine whether the LSD stimulus generalizes to the new test compound. If stimulus generalization occurs (i.e., the animals respond as if they had been given the training drug after administration of the test drug), it may be inferred that the test drug has pharmacological properties similar to the training drug (e.g., LSD). Animals can then be trained with the new drug and tests may be carried out to determine whether the new drug stimulus generalizes to the original training drug. In that event, symmetrical substitution is said to occur, and the inference that LSD and the new drug have similar or identical pharmacology is very strong. Various antagonists can be used to block the discriminative task, and depending on their degree of receptor selectivity, one can reach fairly strong conclusions about which receptor is the target of the training drug. For psychedelics, there is a reasonably good correlation between potency in rat drug discrimination and human potency (Nichols, 2004). False positives can occur, where stimulus generalization occurs with the test drug, when it actually differs in pharmacology from the training drug. When psychedelics are used as training drugs, however, false positives are rare.

HTR

Psychedelics evoke a HTR in mice, which is a paroxysmal rotational movement of the head (Corne & Pickering, 1967) and one of the best characterized of the psychedelic-induced stereotypies. Importantly, mice are inexpensive compared to other laboratory animals and, as contrasted with drug discrimination methods, the HTR does not require the animals to be trained. There is extensive evidence that the 5-HT_{2A} receptor mediates the psychedelic-induced HTR. The first evidence for a linkage between 5-HT_{2A} receptors and the HTR induced by psychedelics was the finding that the potencies of 19 5-HT antagonists to block the mescaline-induced mouse HTR is significantly correlated (r = .88) with their 5-HT_2 affinity (Leysen, Niemegeers, Van Nueten, & Laduron, 1982). Similar findings were later reported for the HTR induced by DOI (Schreiber et al., 1995). It also was demonstrated that ketanserin blocks the HTR to DOI (Darmani, Martin, Pandey, & Glennon, 1990). The HTR to DOI is completely blocked by *M100907,* a highly selective 5-HT_{2A} receptor antagonist, but not by the 5-HT_{2C} antagonist *SB 242,084,* confirming that the behavior is mediated by 5-HT_{2A} receptors (Vickers et al., 2001). Further evidence for a link between 5-HT_{2A} receptors and head twitch was provided by the finding that hallucinogens do not induce the HTR in 5-$HT_{2A}^{-/-}$ knockout mice (Gonzalez-Maeso et al., 2007; Halberstadt, Koedood, Powell, & Geyer, 2011). Nevertheless, several drugs that can induce HTR do not activate the 5-HT_{2A} receptor, and some drugs that are reported to be nonhallucinogenic 5-HT_{2A} receptor agonists also can induce the HTR. Therefore, the HTR can only be used as a proxy for 5-HT_{2A} receptor activation and is not representative of interoceptive hallucinatory or psychedelic effects (Canal & Morgan, 2012).

Exploratory and Investigatory Behavior

In conventional open-field locomotor testing, hallucinogens produce inconsistent re-

sults that do not distinguish between the effects of hallucinogens and nonhallucinogenic agents (Brimblecombe, 1963; Cohen & Wakeley, 1968; Kabes, Fink, & Roth, 1972; Silva & Calil, 1975). The Behavioral Pattern Monitor (BPM), a combination of activity and holeboard chambers, was designed to overcome the shortcomings of open field measurements (Geyer, Russo, & Masten, 1986). The BPM provides both quantitative and qualitative measures of unconditioned locomotor and investigatory activity in rats and can be used to assess animals for changes in responsivity to environmental stimuli.

Psychedelics produce a characteristic profile of behavioral effects in the BPM. When phenylalkylamine (mescaline, DOM, DOI, and DOET) and indolealkylamine (psilocin, DMT, and 5-MeO-DMT) hallucinogens are tested in a novel environment, they decrease locomotor and investigatory behaviors (rearings and holepokes) and increase avoidance of the center of the chamber (Adams & Geyer, 1985a; Krebs-Thomson, Ruiz, Masten, Buell, & Geyer, 2006; Wing, Tapson, & Geyer, 1990). These effects have been attributed to exacerbation of the neophobia and agoraphobia normally exhibited by rats. When animals are tested in a familiar environment, these effects are not observed. LSD has similar effects on investigatory behavior and center entries (Adams & Geyer, 1985b), but it produces a biphasic locomotor pattern, with activity that initially is suppressed, then increases as time progresses (Mittman & Geyer, 1991).

M100907, but not the 5-$HT_{2C/2B}$ antagonist *SER-082,* can block most of the behavioral effects of DOI in the BPM paradigm, which are therefore likely mediated by activation of 5-HT_{2A} receptors (Krebs-Thomson, Paulus, & Geyer, 1998). The pharmacology of the indoleamines is more complex. For example, both the mixed 5-HT_1/β-adrenergic antagonist propranolol (Mittman & Geyer, 1991), and the selective 5-HT_{1A} antagonist *WAY-100635* (Krebs-Thomson & Geyer, 1998) block the initial LSD-induced suppression of locomotor activity, whereas the delayed LSD-induced hyperactivity is blocked by *M100907* (Ouagazzal, Grottick, Moreau, & Higgins, 2001) and the 5-HT_2 antagonist ritanserin (Mittman & Geyer, 1991). By contrast, the behavioral effects of 5-MeO-DMT are antagonized by *WAY-100635* but not by *M100907* (Krebs-Thomson et al., 2006), indicating a predominant role for 5-HT_{1A} receptors.

The 5-HT_{2C} Receptor

Phenylalkylamine and indoleamine hallucinogens also bind to 5-HT_{2C} receptors with high-affinity and functionally are relatively nonselective for 5-HT_{2A} versus 5-HT_{2C} receptors (Nelson, Lucaites, Wainscott, & Glennon, 1999; Porter et al., 1999). The discovery that hallucinogens interact with 5-HT_{2C} receptors confounded the hypothesis that activation of "5-HT_2 receptors" is the primary mechanism by which LSD-like drugs act (Glennon et al., 1984). This hypothesis was proposed prior to the discovery of 5-HT_{2C} sites and was partially based on evidence demonstrating that ketanserin and other classical 5-HT_2 antagonists block the behavioral effects of hallucinogens in various animal paradigms. Unfortunately, many of the early serotonin antagonists are now known to bind at both 5-HT_{2A} and 5-HT_{2C} sites. For example, the antagonist ketanserin is selective for 5-HT_{2A} receptors in humans but is nonselective between 5-$HT_{2A/C}$ in rodents, where many of the pharmacological studies of psychedelics have been and continue to be performed. The potent action of hallucinogens at both 5-HT_{2A} and 5-HT_{2C} receptors led some authors to speculate that hallucinogenesis may be mediated by interactions with both of these receptor populations (Glennon, 1990; Titeler et al., 1988). Indeed, Sanders-Bush and others had even suggested that 5-HT_{2C} receptor occupation plays a primary mechanistic role in the action of hallucinogenic drugs (Burris, Breeding, & Sanders-Bush, 1991).

There is a significant correlation between the affinities of phenylalkylamine hallucinogens for 5-HT_{2C} receptors and their potencies to evoke psychoactive effects in humans and to substitute in DOM-trained animals (Titeler et al., 1988). That can be explained by the fact that 5-HT_{2A} and 5-HT_{2C} receptors display parallel structure–activity relationships for ligand binding (Nelson et al., 1999), so it is possible that the observed correlation between 5-HT_{2C} receptor affinity and hallucinogen potency merely reflects a correlation between affinities of 5-HT_{2A}

and 5-HT_{2C} ligands. Importantly, for a series of structurally diverse 5-HT_2 antagonists, the rank order of potencies for blocking LSD-like stimulus effects (Fiorella et al., 1995) and DOI-induced HTR (Schreiber et al., 1995) does not parallel their 5-HT_{2C} affinity. These findings strongly indicate that interactions with 5-HT_{2C} receptors are not primarily responsible for mediating the behavioral effects of hallucinogens. Furthermore, 5-$HT_{2C/2B}$ antagonists (e.g., *SB 200,646A, SB 206,553,* and *SER-082*) and the selective 5-HT_{2C} antagonist *SB 242,084,* consistently fail to block the effects of hallucinogens in a variety of behavioral paradigms (Halberstadt et al., 2016; Ouagazzal et al., 2001; Schreiber et al., 1994; Sipes & Geyer, 1995; Smith et al., 1999; Wettstein, Host, & Hitchcock, 1999; Winter, Rice, Amorosi, & Rabin, 2007). Although some findings suggesting that 5-HT_{2C} receptor interactions may contribute to or modify the effects of some hallucinogens have occasionally been reported (Krebs-Thomson et al., 1998, 2006; Smith, Barrett, & Sanders-Bush, 2003), the vast majority of evidence demonstrates that the behavioral effects of these drugs are not dependent on the 5-HT_{2C} receptor.

A Role for the 5-HT_{1A} Receptor?

The 5-HT_{1A} receptor was the first of the many serotonin receptors to be cloned and characterized (Kobilka et al., 1987). In the brainstem, 5-HT_{1A} receptors are expressed presynaptically on cells in the dorsal and median raphe nuclei, where they act as somatodendritic autoreceptors to inhibit cell firing. The presynaptic 5-HT_{1A} receptors expressed on raphe cells couple to $G\alpha_{i/o}$ proteins that activate inwardly rectifying potassium channels (GIRKs), causing neuronal membrane hyperpolarization (Aghajanian, 1995), which leads to a decreased rate of cell firing. Following the characterization of the 5-HT_{1A} receptor, LSD and indoleamines were found to be potent agonists at this receptor type. Thus, the raphe cell suppression by LSD and indoleamines discussed earlier could be attributed to their agonist activity at presynaptic 5-HT_{1A} receptors.

Furthermore, the effects of LSD and 5-MeO-DMT in the BPM are partially mediated by the 5-HT_{1A} receptor. There is also considerable evidence that the 5-HT_{1A} receptor plays a role in the discriminative stimulus effects of LSD and 5-MeO-DMT. For example, in mice trained to discriminate LSD from saline, the 5-HT_{1A} receptor antagonist *WAY 100635* produced a 50% blockade of the LSD drug lever selection (Benneyworth, Smith, Barrett, & Sanders-Bush, 2005). In rats, LSD elicits intermediate levels of drug lever selection in animals trained with the 5-HT_{1A} agonist *8-OH-DPAT,* and the 5-HT_{1A} agonist ipsapirone elicits partial substitution in LSD-trained animals (Arnt, 1989). Likewise, the LSD stimulus completely generalizes to the mixed 5-HT_{1A} agonist/α_2-adrenoceptor antagonist yohimbine (Colpaert, 1984; Marona-Lewicka & Nichols, 1995). Ipsapirone and *8-OH-DPAT* produce full substitution in animals trained with 5-MeO-DMT (Schreiber & de Vry, 1993; Spencer, Glaser, & Traber, 1987; Winter, Filipink, Timineri, Helsley, & Rabin, 2000). Indeed, it has been reported that *WAY-100635* and the mixed 5-HT_{1A}/β-adrenergic antagonist pindolol are more effective than pirenperone and ketanserin at blocking stimulus control by 5-MeO-DMT, indicating that the 5-MeO-DMT discriminative stimulus involves a substantial 5-HT_{1A} receptor-mediated component (Spencer et al., 1987; Winter et al., 2000). These observations are consistent with evidence that the behavioral response to 5-MeO-DMT in rodents is mediated predominantly by the 5-HT_{1A} receptor (Halberstadt et al., 2011; Krebs-Thomson et al., 2006; Tricklebank, Forler, Middlemiss, & Fozard, 1985). In addition, as noted earlier, psychedelics suppress raphe cell firing in the brain stem either directly (LSD and indoleamine compounds) or indirectly (by phenethylamines), an effect that also could lead to cortical cell excitation. As demonstrated by Puig, Artigas, and Celada (2005), electrical stimulation of the raphe increases serotonin release into cortical terminal fields, where it activates 5-HT_{1A} receptors on the axon hillock of pyramidal cells, resulting in hyperpolarization. Thus, it seems possible that direct 5-HT_{2A} receptor activation of cortical pyramidal cells could be synergistic with reduced release of serotonin in cortical terminal fields from hallucinogen-induced decreased raphe cell firing. That could be one pharmacological feature

that differs between phenethylamine- and indoleamine-type psychedelics.

Pokorny and colleagues (2016) assessed the potential interaction between psilocybin and the 5-HT_{1A} partial agonist buspirone. Subjects treated with 20 mg buspirone orally (p.o.) prior to a moderate dose of psilocybin (0.17 mg/kg p.o.) showed a significant diminution of effects on the visionary restructuralization (VR) dimension of the Five-Dimensional Altered States of Consciousness Questionnaire (5D-ASC), especially on the item clusters related to elementary and complex visual hallucinations. Although buspirone did not attenuate the effect of psilocybin on the OB dimension, buspirone did reduce the effect of psilocybin on several oceanic boundlessness (OB) dimension item clusters (positive depersonalization, positive derealization, altered sense of time, positive mood, and mania-like experiences). These results are consistent with evidence that the 5-HT_{1A} receptor can modulate 5-HT_{2A}-induced responses.

By contrast, there is evidence that activation of 5-HT_{1A} receptors can inhibit 5-HT_{2A} receptor-induced behavioral effects. Pretreatment with the 5-HT_{1A} agonist *8-OH-DPAT* dose-dependently attenuated the HTR to DOI in rats and mice (Arnt & Hyttel, 1989; Berendsen & Broekkamp, 1990; Darmani et al., 1990) and the reciprocal hindleg body scratch induced by DOI in the gerbil (Eison & Wright, 1992). The LSD analogue lysergic acid morpholide (LSM-775) does not induce head twitches in mice unless administered in combination with the 5-HT_{1A} antagonist *WAY-100635,* indicating that 5-HT_{1A} activation by LSM-775 masks its ability to induce the HTR (Brandt et al., 2018). Similarly, the mixed 5-$HT_{1A/1B/}$β-adrenergic antagonist pindolol was used to assess the involvement of 5-HT_{1A} receptors in the response to DMT (Strassman, 1996). Pretreatment with pindolol intensified the subjective effects of DMT, suggesting that activation of 5-HT_{1A} receptors by DMT acts to attenuate the psychedelic effects of the drug.

MDMA

3,4-Methylenedioxymethamphetamine (MDMA; ecstasy) is a novel substituted amphetamine that has some similarity in its effects to phenethylamine psychedelics. It also has been claimed to have value as an adjunct to psychotherapy. MDMA produces mood elevation and an increased sense of empathy, with little sensory disruption. The effects of MDMA are distinct from those typically produced by psychedelics, however, and it has been proposed that MDMA is an entactogen, a distinct class of drugs (Nichols, 1986; Nichols, Hoffman, Oberlender, Jacob, & Shulgin, 1986). MDMA has been demonstrated to have promise in the treatment of patients with posttraumatic stress disorder (PTSD) (Sessa, 2017, 2018), and is now entering U.S. Food and Drug administration (FDA)–approved Phase 3 clinical studies. Its primary mechanism of action is indirect, by activation of serotonin receptors through release of 5-HT from presynaptic terminals. In addition, MDMA also induces release of dopamine and norepinephrine from presynaptic neuron terminals; it is unclear what contribution(s) the catecholamines make to the overall effect of MDMA. Nonetheless, the uniqueness of the psychopharmacology of MDMA compared to other structurally similar stimulants such as methamphetamine is apparently due to the addition of the robust serotonergic component.

Clinical Pharmacology of Psychedelics

In the past three decades, there has been renewed interest in the possibility that psychedelics may be useful therapeutic drugs. In order to assess the acute clinical effects of psychedelics, one requires appropriate instruments to characterize and quantify changes in consciousness. Common psychedelic effects can be reliably measured using validated psychometric instruments consisting of self-report questionnaires and rating scales. The most widely used and validated instrument for that is the Altered States of Consciousness (APZ) Rating Scale (Dittrich, 1998). It measures three primary and one secondary dimension of altered states of consciousness (ASCs) that are believed to be invariant across types of ASC induction methods. This self-administered questionnaire was developed by Adolph Dittrich (1998) to assess alterations of consciousness

in an etiology-independent manner. Numerous clinical trials have confirmed that the APZ Rating Scale is sensitive to the effects of psychedelics, including psilocybin, DMT, ayahuasca, mescaline, and LSD (Gouzoulis-Mayfrank et al., 1999, 2005; Hermle et al., 1992; Liechti, Dolder, & Schmid, 2017; Riba, Rodriguez-Fornells, & Barbanoj, 2002; Vollenweider et al., 1997, 1998).

Dittrich proposed that the subjective effects of hallucinogens could be divided into three major dimensions: (1) "oceanic boundlessness" (OB), (2) "anxious ego dissolution" (AED), and (3) "visionary restructuralization" (VR). The OB dimension is similar to classical mystical experiences and involves a pleasant state of depersonalization and derealization. The AED dimension incorporates dysphoric effects such as anxiety, thought disorder, delusions, fear of losing control, and ego disintegration. The VR dimension includes perceptual phenomena such as visual hallucinations and illusions, synesthesia, and changes in the meaning of percepts. The OB, AED, and VR dimensions contain multiple clusters of items from the APZ questionnaire. Studies that employed an updated version of the APZ, the 5D-ASC, have shown that psilocybin and LSD also increase scores in a dimension known as "reduction of vigilance" (RV), which includes measures of drowsiness, cognitive impairment, and decreased alertness (Carter et al., 2007; Hasler, Grimberg, Benz, Huber, & Vollenweider, 2004; Liechti et al., 2017; Vollenweider, Csomor, Knappe, Geyer, & Quednow, 2007). A fluorodeoxyglucose [^{18}F]FDG PET study demonstrated that psilocybin increases cerebral glucose metabolic activity in PFC, anterior cingulate, temporomedial cortex, and putamen, and the increased metabolic rate within those regions was found to be significantly correlated with subjective effects in the OB, VR, and AED dimensions (Vollenweider et al., 1997).

The Hallucinogen Rating Scale (HRS) is another instrument that has been used to assess the subjective effects of hallucinogens. The HRS contains 99 items in six clusters: (1) *Somaesthesia* (interoceptive effects), (2) *Affect* (changes in mood and emotion), (3) *Perception* (visual, auditory, tactile, and olfactory experiences), (4) *Cognition* (modification of thought and cognitive processes), (5) *Volition* (the degree to which the subject is incapacitated by the drug), and (6) *Intensity* (overall strength of the drug effect). Although the HRS was designed specifically to measure the response to intravenous DMT (Strassman, Qualls, Uhlenhuth, & Kellner, 1994), it also has been employed in studies of ayahuasca (Riba, Rodriguez-Fornells, Strassman, & Barbanoj, 2001; Riba et al., 2003), psilocybin (Gouzoulis-Mayfrank et al., 1999; Griffiths et al., 2011; Griffiths, Richards, McCann, & Jesse, 2006), and 2,5-dimethoxy-4-bromophenethylamine (2C-B; Papaseit et al., 2018).

After a hiatus of more than 20 years, the first clinical studies of a psychedelic were reported by Strassman (Strassman & Qualls, 1994; Strassman, Qualls, & Berg, 1996; Strassman et al., 1994). These studies focused on basic physiological and hormonal changes following intravenous injection of different doses of DMT fumarate, and no attempt was made to assess its potential therapeutic actions. Interestingly, at the highest doses, subjects reported encounters with "alien" beings and landscapes, which led to a book and a movie by Strassman (2001) titled *DMT: The Spirit Molecule*.

The first modern attempt to identify a therapeutic use for a psychedelic was a study of the efficacy of psilocybin in the treatment of obsessive–compulsive disorder (OCD) (Moreno, Wiegand, Taitano, & Delgado, 2006). Nine subjects diagnosed with OCD were given a total of 29 doses of psilocybin, including a low, a medium, and a high dose in a double-blind procedure that lacked a placebo control. Marked but variable decreases in symptoms were observed in all subjects during one or more testing sessions. Most subjects experienced symptom reduction beyond 24 hours and beyond the pharmacological half-life of psilocybin, but only one subject reported symptom reduction at 6 months. These promising results indicate that the utility of psilocybin therapy should be investigated further, using a larger number of participants in a standard randomized controlled trial.

That same year, Griffiths and colleagues (2006), at Johns Hopkins University, reported on effects of psilocybin in normal volunteers. Thirty hallucinogen-naive adult volunteers reporting regular participation in

religious or spiritual activities were enrolled in the study. Two or three sessions were conducted at 2-month intervals in which volunteers received orally administered psilocybin (30 mg/70 kg) and methylphenidate hydrochloride (40 mg/70 kg) in counterbalanced order. Psilocybin produced a range of acute perceptual changes, subjective experiences, and labile moods. Psilocybin also increased measures of mystical experience. At 2 months, 67% of the volunteers rated the experience with psilocybin to be either the single most meaningful experience of their lives or among the top five most meaningful experiences of their lives. Thirty-three percent of the volunteers rated the psilocybin experience as being the single most spiritually significant experience of their lives, with an additional 38% rating it to be among the top five most spiritually significant experiences.

At the 14-month follow-up, 58 and 67%, respectively, of volunteers rated the psilocybin-occasioned experience as being among the five most personally meaningful and among the five most spiritually significant experiences of their lives. Of the volunteers, 64% indicated that the experience increased their well-being or life satisfaction, and 58% met criteria for having had a "complete" mystical experience. Correlation and regression analyses indicated a central role of the mystical experience assessed on the session day in the high ratings of personal meaning and spiritual significance at follow-up (Griffiths, Richards, Johnson, McCann, & Jesse, 2008). It had been known since the 1960s that psychedelics can induce mystical and spiritual experiences (Pahnke, 1969; Pahnke & Richards, 1966), but this work documented significant positive, long-term benefits to the use of psychedelics in normal volunteers.

In a similar follow-up study (Griffiths et al., 2011), participants were 18 adults, 17 of whom were hallucinogen naïve. Five 8-hour sessions were conducted individually for each participant at 1-month intervals. Participants were randomized to receive the four active doses in either ascending or descending order (nine participants each). This double-blind study evaluated psilocybin at 0, 5, 10, 20, and 30 mg/70 kg (p.o.). Placebo was scheduled quasi-randomly. One month after sessions at the two highest doses, volunteers rated the psilocybin experience as having substantial personal and spiritual significance, and attributed to the experience sustained positive changes in attitudes, mood, and behavior, with the ascending dose sequence showing greater positive effects.

Results from these two Griffiths studies were then combined and analyzed by MacLean, Johnson, and Griffiths (2011). They reported potential changes in five generally recognized broad personality domains: neuroticism, extroversion, openness, agreeableness, and conscientiousness. Personality change was assessed 1–2 months after a high-dose psilocybin session and again more than 1 year later to determine the persistence of personality change. Although there were no significant changes in the personality domains of neuroticism, extroversion, agreeableness, or conscientiousness, the trait of openness increased significantly from screening to posttest. Taken together, their results indicate predominantly stable personality traits, but with specific increases in openness following the high-dose psilocybin session.

MacLean and colleagues (2011) further examined the relationship between mystical experience and increases in openness by comparing participants who met the criteria for having had a complete mystical experience during their high-dose session with participants who did not meet the criteria. ANOVA revealed a significant interaction between time (screening vs. posttest) and group (complete mystical experience vs. no complete mystical experience). Follow-up *t*-tests confirmed that the complete mystical experience group showed significant increases in openness from screening to posttest. They observed a significant linear correlation between the degree of mystical experience and change in openness. Interestingly, openness includes a relatively broad range of intercorrelated traits covering aesthetic appreciation and sensitivity, fantasy and imagination, awareness of feelings in self and others, and intellectual engagement. People with high levels of openness are "permeable to new ideas and experiences" and "motivated to enlarge their experience into novel territory" (see references in MacLean

et al., 2011). Openness is also strongly associated with creativity, and some of its facets are correlated with general fluid intelligence and cognitive ability.

In another study by Griffiths and colleagues (2018) psilocybin was administered in a double-blind paradigm to 75 healthy participants who undertook a program of meditation/spiritual practices. Healthy participants were randomized to three groups of 25 each: (1) very low dose (1 mg/70 kg on Sessions 1 and 2) with moderate-level ("standard") support for spiritual practice (LD-SS); (2) high dose (20 and 30 mg/70 kg on Sessions 1 and 2, respectively) with standard support (HD-SS); and (3) high dose (20 and 30 mg/70 kg on Sessions 1 and 2, respectively) with high support for spiritual practice (HD-HS). Psilocybin was administered 1 and 2 months after spiritual practice initiation. Outcomes at 6 months included rates of spiritual practice and persisting effects of psilocybin. Compared with low-dose, high-dose psilocybin produced greater acute and persisting effects. At 6 months, compared with LD-SS, both high-dose groups showed large, significant positive changes on longitudinal measures of interpersonal closeness, gratitude, life meaning/purpose, forgiveness, death transcendence, daily spiritual experiences, religious faith and coping, and community observer ratings. The authors concluded that a mystical experience and/or its neurophysiological or other correlates are likely determinants of the enduring positive attitudinal, dispositional, and behavioral effects of psilocybin when administered under spiritually supported conditions. Recent studies by Liechti and colleagues (2017) and Schmid and Liechti (2018) indicated similar benefits resulting from LSD-induced mystical experiences.

Recently, antidepressant and anxiolytic effects in patients with terminal cancer have been demonstrated in clinical trials (Griffiths et al., 2016; Grob et al., 2011; Ross et al., 2016). In addition, in small pilot studies, psilocybin-assisted therapy has shown promise for disruption of addiction to alcohol (Bogenschutz et al., 2015) and nicotine (Johnson, Garcia-Romeu, Cosimano, & Griffiths, 2014; Johnson, Garcia-Romeu, & Griffiths, 2017). In the studies assessing the efficacy of psilocybin as a potential treatment for anxiety and depression in patients with cancer and tobacco addiction, the therapeutic response was correlated with the intensity of psilocybin-induced mystical experience.

Mechanism of Psychedelic Effects in Humans

As part of a series of studies of the effects of psilocybin in human volunteers, Vollenweider and colleagues (1998) assessed the effect of pretreatment with the 5-HT_{2A} antagonist ketanserin, the mixed D_2/5-HT_{2A} antagonist risperidone, and the dopamine (D_2) antagonist haloperidol. The effects of psilocybin on the OB, AED, and VR dimensions of the APZ were reduced by pretreatment with 20 mg ketanserin (p.o.) and almost completely blocked by pretreatment with either 40 or 50 mg ketanserin (Carter et al., 2007; Vollenweider et al., 1998). Likewise, pretreatment with 0.5 and 1.0 mg risperidone (p.o.) produced partial and complete blockade, respectively, of the subjective effects of psilocybin (Vollenweider et al., 1998). Conversely, haloperidol was much less effective, producing only partial blockade of psilocybin effects in the OB dimension, while actually increasing scores in the AED dimension. Taken together, these findings confirm that the hallucinogenic effects of psilocybin in humans are primarily mediated by actions at the 5-HT_{2A} receptor, with D_2 receptor interactions playing only a minor role.

Vollenweider and colleagues also have examined whether the neurophysiological effects of psilocybin are affected by 5-HT_{2A} receptor blockade. Reductions in N170 visual-evoked potentials and α oscillatory activity in visual cortex are thought to play an important role in the visual hallucinations produced by psilocybin and other hallucinogens (Kometer & Vollenweider, 2018). Thus, it is notable that ketanserin completely blocks the effect of psilocybin on N170 potentials and α oscillations (Kometer et al., 2013), consistent with the absence of psilocybin-induced visual hallucinations in subjects pretreated with ketanserin (Carter et al., 2007; Vollenweider et al., 1998). Pretreatment with ketanserin also reportedly attenuates the reduction of prepulse inhibition

(PPI) produced by psilocybin (Quednow, Kometer, Geyer, & Vollenweider, 2012).

Several fairly recent studies have examined whether ketanserin also can block the effects of LSD in human subjects. As found previously with psilocybin, 40 mg ketanserin (p.o.) pretreatment completely blocked the subjective effects produced by 100 μg (p.o.) doses of LSD free base (Kraehenmann, Pokorny, Aicher, et al., 2017; Kraehenmann, Pokorny, Vollenweider, et al., 2017; Preller et al., 2017). Ketanserin fully inhibited the misattribution of personal relevance observed in subjects administered LSD, as well as the BOLD signal increase induced by LSD in frontal cortical areas involved in self-referential processing (Preller et al., 2017). Furthermore, ketanserin blocked the ability of LSD to increase *primary process thinking* (a dreamlike cognitive state characterized by seemingly unorganized sequences of thoughts and images) in subjects performing a guided mental imagery task (Kraehenmann, Pokorny, Aicher, et al., 2017).

In an fMRI study, Barrett, Preller, Herdener, Janata, and Vollenweider (2018) examined the effect of LSD on music processing in the brain. The relationships between the 24 major and minor keys of Western tonal music (e.g., how many notes they have in common, their relative perceptual "fit") can be represented on the surface of a torus (Krumhansl, 1990; Krumhansl & Kessler, 1982; Toiviainen & Krumhansl, 2003). As music progresses, the sequence of melodies and chord progressions creates specific patterns of activity on the toroidal surface. According to previous fMRI studies, these activity patterns in tonal space are tracked in the rostromedial PFC and other cortical regions (Janata, 2005; Janata et al., 2002), a phenomenon known as *tonality tracking*. Administration of LSD (100 μg p.o.) enhanced tonality tracking in medial PFC, superior temporal gyrus, inferior temporal gyrus, angular gyrus, and amygdala, brain regions involved in processing speech and music, as well as associated autobiographical and emotional responses (Barrett et al., 2018). Most of the effects of LSD on tonality tracking were blocked when subjects were pretreated with ketanserin (40 mg p.o.), consistent with the involvement of 5-HT_{2A} receptors.

As noted earlier, ayahuasca is a brew prepared from a mixture of plants. *Banisteriopsis caapi* vines, which contain β-carboline alkaloids such as harmine and harmaline, are extensively boiled together with leaves of *Psychotria viridis,* which contain DMT (McKenna et al., 1984; Schultes & Hofmann, 1980). Although DMT is not orally active due to first-pass metabolism (Szara, 1957; Turner & Merlis, 1959), the β-carboline alkaloids act as reversible inhibitors of liver MAO, allowing DMT to possess oral activity. Similar to other psychedelics, administration of ayahuasca to human subjects reduces alpha oscillatory activity in occipital and parietal cortices (Riba, Anderer, Jane, Saletu, & Barbanoj, 2004; Schenberg et al., 2015; Valle et al., 2016). As with psilocybin and LSD, pretreatment with ketanserin (40 mg p.o.) blocks the effect of ayahuasca on alpha activity (Valle et al., 2016). Interestingly, however, ketanserin only partially attenuated the subjective experience produced by a dose of ayahuasca containing 0.75 mg/kg DMT. Therefore, although 5-HT_{2A} receptor agonist activity can fully account for the subjective effects of psilocybin and LSD (see earlier discussion), the same may not be true for ayahuasca. In addition to inhibiting MAO, the beta-carboline alkaloids in ayahuasca can interact with a variety of molecular targets and recognition sites, including voltage-dependent Na^+ channels (Deecher et al., 1992), imidazoline I_2 sites (Husbands et al., 2001), dual-specificity tyrosine phosphorylated and regulated kinase 1A (DYRK1A) (Bain et al., 2007), *N*-methyl-D-aspartate (NMDA) receptors (Du, Aloyo, & Harvey, 1997), and the σ_1 receptor (Bowen et al., 1995). Further studies are required to characterize fully the receptor mechanisms responsible for ayahuasca-induced phenomenology.

Although other chapters in this volume deal extensively with how psychedelics affect brain dynamics, it may be helpful here to comment briefly on this topic. We have noted that psychedelics depolarize cortical cells, and that action potentials are generated in claustral glutamate cells. Claustral projections are widespread throughout the brain, so the generation of action potentials that release glutamate onto already-sensitized cortical cells would be expected to pro-

duce changes in brain dynamics. We have recently proposed that claustral cell firing may be catalytic in engendering changes in resting state network communication (Nichols, Johnson, & Nichols, 2017). Recent studies using BOLD fMRI and magnetoencephalography (MEG) imaging methods after psychedelic administration in humans have given powerful insight into the networks that the brain employs for communication (Barrett et al., 2018; Carhart-Harris et al., 2012, 2016; Muthukumaraswamy et al., 2013; Preller et al., 2017, 2018; Tagliazucchi et al., 2016). In essence, the brain can be thought of as comprising anatomically distinct regions called nodes or hubs. Normally, communication occurs mostly within these nodes (i.e., integration), which are largely (but not completely) segregated from other nodes. After a psychedelic, however, the integration within, and segregation between different nodes is lost, and new communication networks are formed that allow widespread (global) communication between many other nodes or hubs. One of the key hubs that is disrupted is the DMN. This network is normally highly organized and active when a person is not carrying out a mental task. It has been proposed that collapse of integrity within the DMN leads to "ego loss" and the mystical experience after taking a psychedelic (Carhart-Harris et al., 2014; Tagliazucchi et al., 2016). Thus, 5-HT_{2A} receptor agonism leads to desynchronization of oscillatory activity, disintegration of intrinsic integrity in the DMN and related brain networks, and an overall brain dynamic characterized by increased between-network global functional connectivity, expanded signal diversity, and a larger repertoire of structured neurophysiological activation patterns. Crucially, these characteristic traits of psychedelic brain activity have been correlated with the phenomenological dynamics and intensity of subjective psychedelic effects (Swanson, 2018).

Psychedelics as Anti-Inflammatory Agents

The protein target of psychedelics, the 5-HT_{2A} receptor, is the most widely expressed serotonin receptor throughout the mammalian body. It is found in nearly all cell types of every organ. These include epithelial, endothelial, muscle, and immune-related cells. Despite that, nearly all research into the function of this receptor has focused on the CNS and its role in brain activity and behavior. Given the near ubiquitous expression of this receptor, it was somewhat unexpected that the genetic knockout mouse was found to be relatively normal. Furthermore, there are no known diseases associated with polymorphisms or mutations in the *HTR2A* gene locus. One potential role identified for this receptor in the periphery was as a participant in serotonin-mediated inflammation. Serotonin has long been recognized as a mediator of inflammation, and its levels have been found to be elevated at sites of inflammation (Shajib & Khan, 2015). Antagonists of the 5-HT_{2A} receptor have been shown to have anti-inflammatory effects in several animal models (Hayashi et al., 2003; Nishiyama, 2009). The anti-inflammatory effect of antagonists is presumably achieved by blocking the proinflammatory effects of serotonin itself on the target tissues, and prevention of activation of 5-HT_{2A} receptors. Interestingly, certain polymorphisms in the *HTR2A* gene locus have been associated with a protective effect against certain inflammatory disorders (Snir et al., 2013).

Therefore, it was a surprising discovery when one of us (C. D. N.) found that psychedelics are capable of producing an extremely potent anti-inflammatory effect: specifically, that psychedelics can prevent the inflammatory response induced by tumor necrosis factor-α (TNF-α) in cultures of cells isolated from vascular tissues (Yu et al., 2008). Several psychedelics were tested, including LSD, with a potency to block inflammation about that of corticosteroids for their targets. One drug, (*R*)-DOI, was especially potent and blocked TNF-α-mediated inflammation at much lower concentrations of the drug. The structural basis for the superpotency of (*R*)-DOI to inhibit inflammation compared to other psychedelics like LSD is not yet known, but it is the subject of active study.

Significantly, the ability of psychedelics to block inflammation in cell culture was translated to the whole animal. A single pretreatment with low subbehaviorally active doses of (*R*)-DOI was able to block completely the

inflammation produced by systemic injection of TNF-α in mice (Nau, Yu, Martin, & Nichols, 2013). That included prevention of increased intercellular adhesion molecule 1 (ICAM1), vascular cell adhesion molecule 1 (VCAM1), interleukin 1b (IL1b), and monocyte chemoattractant protein-1 (MCP1) in tissues and interleukin 6 (IL6) in tissues and circulation (Nau et al., 2015). Moving to a rodent model of a human inflammatory disease, allergic asthma, a psychedelic once again proved to be a potent anti-inflammatory. In this model, (*R*)-DOI is able to prevent the hallmark symptoms of asthma, including airways hyperresponsiveness, eosinophilia, mucus overproduction, and recruitment of activated T helper 2 (Th2) cells to the lung at subbehavioral doses (Nau et al., 2015). Additionally, bronchial inflammation is suppressed, as are levels of inflammatory cytokines and chemokines in the lung of sensitized animals exposed to allergens (Nau et al., 2015). Further work has established that several other psychedelics in addition to (*R*)-DOI can potently suppress the development of asthma, whereas other psychedelics are less potent, in both mouse and rat models of allergic asthma (unpublished data C. D. N.). These compounds and assays are currently being utilized to examine functionally selective mechanisms downstream of receptor activation leading to behavioral and/or anti-inflammatory pathways.

The anti-inflammatory effects of additional psychedelics and 5-HT_{2A} receptor agonists have been reported. The primary psychedelic component of ayahuasca, mentioned earlier, is DMT. Recently, there have been reports that this decoction has anti-inflammatory properties that are mediated through the σ-1 receptor (Szabo, Kovacs, Frecska, & Rajnavolgyi, 2014; Szabo et al., 2016). DMT was shown to reduce proinflammatory cytokine expression in human induced pluripotent stem cell (iPSC)–derived cortical neuron- and microglia-like cells in culture, and RNA interference (RNAi) knockdown of the σ-1 receptor gene eliminated these anti-inflammatory effects (Szabo et al., 2014, 2016). It remains to be seen, however, whether these interesting results can be translated to animal models of inflammation. In another relatively recent study, extracts of Australian cane toad skins were tested for anti-inflammatory effects in a human monocyte cell line, and were found to suppress lipopolysaccharide (LPS)–induced expression of several proinflammatory cytokines including TNF-α and IL6 (Zulfiker, Hashimi, Qi, Grice, & Wei, 2016). Although there are many bioactive compounds in the extracts, their positive control was bufotenine, a tryptamine drug related in structure to psilocin that is an agonist of the serotonin 5-HT_{2A} receptor and a major component of the extracts. Bufotenine had roughly the same efficacy as the skin extracts, suggesting that this tryptamine was responsible for the observed anti-inflammatory effects (Zulfiker et al., 2016). Additional experiments will need to be performed to examine whether or not activity at the 5-HT_{2A} receptor is the underlying anti-inflammatory mechanism of bufotenine and the Australian cane toad skin extracts.

Together, these *in vitro* and *in vivo* preclinical data support the idea that psychedelics may one day serve as potent steroid-sparing anti-inflammatory agents for a variety of disorders, including atherosclerosis, asthma, and inflammatory bowel disease. Importantly, levels of drug needed may be several orders of magnitude lower than necessary to influence behaviors.

Psychedelics and Gene Expression

In the late 1960s through the mid-1970s, a series of publications from a few different groups claimed that LSD produced chromosomal damage. Whereas the first of these examined the effects of LSD on leukocytes in culture, subsequent reports claimed chromosomal damage in human users of the drug (Egozcue, Irwin, & Maruffo, 1968; Long, 1972). It is now generally recognized that psychedelics, including LSD, do *not* produce chromosomal damage. They can, however, alter gene expression in their target tissues. Acute changes in expression may impact the immediate subjective experience, and long-lasting changes may underlie their therapeutic potential to treat depression and addiction. Two psychedelics have received significantly more study than others with respect to gene expression: LSD and DOI, the first likely due to its widespread use as

a recreational drug, and the second because it is a selective receptor agonist of 5-HT_2 receptors that has been available as a valuable research tool to explore the pharmacology of this receptor family.

Initial studies using *in situ* hybridization and immunohistochemistry demonstrated that LSD and DOI are able to induce rapidly the expression of immediate early genes (IEGs) and their encoded proteins that include *c-fos* and *arc* in specific regions of rodent brain (Frankel & Cunningham, 2002; Gresch, Strickland, & Sanders-Bush, 2002; Pei et al., 2000; Scruggs, Patel, Bubser, & Deutch, 2000; Tilakaratne & Friedman, 1996). IEGs in general rapidly respond to various stimuli by increasing their messenger RNA (mRNA) expression. The majority, like *c-fos,* encode for a transcription factor that will subsequently activate several downstream target genes, depending on the nature of the stimuli. Interestingly, the cells that had increased IEG expression were not found to be the 5-HT_{2A} receptor expressing neuronal population (Gresch et al., 2002; Pei, Tordera, Sprakes, & Sharp, 2004; Scruggs et al., 2000). Because IEG expression could be blocked by selective 5-HT_{2A} receptor antagonists, it was believed that activation of the unidentified cells with increased IEG expression was indirect. Why the 5-HT_{2A} positive neurons were not seemingly transcriptionally responding remained elusive for several more years.

The first unbiased screen of the effects of a psychedelic, LSD, in rodent brain was reported by Nichols and Sanders-Bush (2002). Using newly developed microarray technology, a single dose of LSD was found to increase only a small cohort of genes in rat PFC. A subsequent screen identified a few more up-regulated genes (Nichols & Sanders-Bush, 2004). Each of these genes had their expression either completely or partially mediated by 5-HT_{2A} receptor activation. The majority were IEGs that had been implicated by others in the process of synaptic plasticity. One previously unknown transcript was identified and named *ilad1* (Nichols & Sanders-Bush, 2004). *Ilad1* and its predicted protein have significant homology to beta arrestin, with two arrestin-like domains for protein–protein interactions. *Ilad1* was subsequently renamed *arrdc2* (arrestin domain containing protein 2) and represented the first member of a new class of proteins later termed α-arrestins (Alvarez, 2008). Of these genes, all were found to return to baseline expression levels within 3 hours with the exception of *nor1,* which remained at maximal levels for at least 5 hours after drug administration (Nichols & Sanders-Bush, 2004). Subsequent microarray screens by González-Maeso and coworkers (2003) identified a similar response in mouse cortical tissues. Interestingly, they noted that different agonists at the receptor could produce differing genetic responses.

The effects of psychedelics on long-term gene expression changes were examined in a new proposed potential rat model of psychosis. In this model, rats administered a low dose of LSD every other day over 6 months developed aberrant behaviors that are conserved with those of other models of psychosis, including increased locomotion, increased reactivity, anhedonia, and aggression (Marona-Lewicka, Nichols, & Nichols, 2011). Remarkably, these abnormal behaviors persisted for at least several weeks after discontinuation of the drug. An RNA-sequencing screen of the PFC of these rats 4 weeks after the final drug administration revealed about 700 genes significantly altered in expression (Martin, Marona-Lewicka, Nichols, & Nichols, 2014). Functional clustering highlighted groups of genes involved in synaptic plasticity, GPCR signaling, and metabolic function, among others (Martin et al., 2014). Furthermore, there was a significant enrichment of genes previously implicated by others in both schizophrenia and bipolar depression (Martin et al., 2014). Although this study examined gene expression after 3 months of drug administration, it highlighted the fact that LSD can influence gene expression for a long time after drug administration has stopped.

More recently, new tools have allowed for the examination of the molecular and genetic responses of individual cell types within the brain that respond to psychedelics (Martin, Xu, Porretta, & Nichols, 2017). With a focus on the medial PFC, a small subpopulation (~3–5%) of neurons was found that directly respond to LSD and DOI with increased IEG expression (Martin & Nichols, 2016). Transcripts that rapidly increased

in expression include *c-fos*, ΔfosB, krox20/erg2, and *per1* (Martin & Nichols, 2016). Rapid and increased IEG expression in neurons highly correlates with depolarization, and these neurons may be similar to those identified earlier by electrophysiology that depolarize in response to 5-HT and 5-HT_{2A} receptor agonists (Beique et al., 2007). All directly activated neurons expressed four times the level of *HTR2A* transcript than was measured for the nonactivated neuronal pool. Therefore, these neurons may be directly responding because they are more sensitive to 5-HT_{2A} receptor agonists due to their increased receptor level compared to the nonresponding neurons. These directly responding neurons, named the trigger population, were discussed earlier. Interestingly, the transcriptional response of the trigger population of neurons differs between brain regions. For example, the immediate early gene *krox20/egr2* was induced in neurons purified from somatosensory cortex but not in neurons purified from the medial PFC. These regional transcriptional differences may underlie differential regional responses to psychedelics that manifest as differences in network connectivity between regions observed by imaging studies.

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